General

Guideline Title

Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation.

Bibliographic Source(s)

Kelly DA, Bucuvalas JC, Alonso EM, Karpen SJ, Allen U, Green M, Farmer D, Shemesh E, McDonald RA. Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl. 2013 Aug;19(8):798-825. [321 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The grading system for the strength of recommendations (1 or 2) and the levels of evidence (A–C) is defined at the end of the "Major Recommendations" field.

Routine Monitoring and Management

Growth and Nutritional Rehabilitation

1. Optimize the nutritional status before and after liver transplantation (LT) (1B).
2. To encourage growth, routine immunosuppression protocols should minimize steroid exposure during the first 6 to 12 months after transplantation (1A).
3. Measure the height and weight to identify patients with growth impairment who may benefit from reduced steroid exposure (1B).
4. Monitor the body mass index and consider obesity management (2C).

Endocrine and Bone Metabolism

Hepatic Osteodystrophy

5. Monitor patients for persistent hepatic osteodystrophy, risk factors for fractures, and scoliosis (1B).
6. Continue mineral and fat-soluble vitamin supplementation (especially D_2, or D_3) until vitamin D levels are normal (1B).

Psychosocial Development

7. The follow-up of school-aged LT recipients should include an assessment of school functioning and school absence (1A).
8. Be aware of posttraumatic stress disorder or other mental health issues and refer a patient for a formal psychiatric evaluation if significant symptoms are present (1B).

Neurocognitive Function

9. Screen neurocognitive function before transplantation for LT candidates older than 5 years and at key junctures afterward to determine special education needs (1B).
10. Assess recipients for hearing loss in the first postoperative year and periodically thereafter as indicated (1B).
11. Provide rehabilitation immediately after transplantation: physical therapy for infants with delayed motor development and speech and occupational therapy for older children with deficits (1B).

Adherence

12. The transplant team assesses and treats nonadherence with a multidisciplinary approach (2B).
13. Screen for nonadherence with objective methods such as the monitoring of immunosuppressant levels (1B).

Screening and Detection of Late Surgical Complications

14. Surgical complications are optimally investigated and treated at a transplant center (2B).

Protocol Liver Biopsy

15. Protocol liver biopsy 1 year after transplantation is not required (1B).

Screening for Skin Cancer

16. Encourage protective clothing, regular screening for skin lesions, and sunscreen (1B).

Safe Living

17. Minimize infection risks related to hygiene, food, water, animals/pets, and travel (2C).
18. Recipients can travel abroad 6 months after transplantation with normal precautions and the advice of their transplant center (2C).
19. Combat childhood infections with recombinant or killed vaccines (1A).
20. Immunize household contacts. Recipients and relatives should receive the annual influenza immunization (1B).

<u>Immunosuppression</u>

Acute Rejection (AR)

21. Serial measurements of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), and immunosuppressant blood levels are the main means of detecting graft dysfunction and AR (1B)
22. A histological assessment of a liver biopsy sample remains the best means of diagnosing AR (1A).

Chronic Rejection (CR)

23. CR is a major cause of late graft loss and should be considered in the setting of poorly responsive AR with biopsy findings supportive of CR (1A).
24. Treat CR with one of a variety of choices: use a higher serum level of the immunosuppressive (e.g., tacrolimus), switch to different immunosuppressives (e.g., from tacrolimus to mTOR inhibitors), and/or add other immunosuppressives (e.g., mycophenolate; 1B).

Renal Function

Screening and Prevention

25. Regularly screen renal function with the estimated glomerular filtration rate (eGFR) and practice calcineurin minimization. Consider renal-sparing drugs when the calculated GFR is <70 mL/minute/1.73 m^2 (1B).

Diabetes Mellitus

26. Screen LT recipients older than 5 years annually with fasting glucose in the early post-LT period and during long-term follow-up. Diagnose and treat posttransplant diabetes mellitus with the current standardized criteria (1A).

Cardiovascular Disease

27. Screen recipients annually for cardiovascular risks (body mass index, blood pressure, and fasting lipids) and treat them according to age specific guidelines. Consider modifying immunosuppression regimens (1B).

Withdrawal of Immunosuppression

28. Corticosteroids may be withdrawn within 6 months of transplantation for patients who receive tacrolimus as their primary immunosuppression (1B).
29. For patients more than 1 year after transplantation with normal liver blood tests, maintain tacrolimus therapy with target immunosuppression levels <6 ng/mL (1C).
30. More than 5 years after transplantation, immunosuppression minimization (defined as a calcineurin inhibitor [CNI] once daily) may be considered if there is no history of CR, liver tests are normal, and a biopsy sample shows minimal or no portal inflammation and less than stage 3 fibrosis (2C).
31. Complete immunosuppression withdrawal may be indicated if there are significant immune-related complications, but this should occur only within clinical trials (2C).

Disease-specific Issues and Recurrent Disease

32. Be aware of the risk of recurrence of primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) in children after transplantation and the need to continue steroids (1B).
33. Periodic screening for colon cancer after transplantation for PSC with colitis may be beneficial; the optimal intervals are unknown (2B).
34. A multidisciplinary approach to hepatoblastoma care involving oncology, radiology, hepatology, and surgery can improve posttransplant survival (2B).
35. Patients with cystic fibrosis require close multispecialist care after isolated LT, with particular attention paid to nutrition, lung function, and infectious risks (1A).

Infections

Late Viral Infections

Cytomegalovirus (CMV)

36. Diagnose with quantitative nucleic acid-based or CMV pp65 antigenemia viral load assays in patients with a compatible clinical syndrome (1A).
37. No specific prophylactic strategy is routinely indicated for CMV donor-negative/recipient-negative children, but the use of intravenous ganciclovir for all CMV donor-positive/recipient-negative recipients is recommended (1A).
38. The primary transplant center should coordinate the management of symptomatic or asymptomatic patients with detectable CMV polymerase chain reaction and/or rising titer CMV viral loads (1B).
39. Intravenous ganciclovir is recommended as the initial antiviral therapy; continue this until the CMV load becomes undetectable (2C).
40. Consider ganciclovir resistance in patients with refractory clinical symptoms or children with persistent/rising CMV loads despite at least 14 days of antiviral therapy. Consider genotypic testing for resistance mutations and second-line therapies (foscarnet and cidofovir; 1B).

Epstein-Barr Virus (EBV) and Post-transplant Lymphoproliferative Disorder (PTLD)

41. Determine the EBV serostatus of recipients and donors to identify patients at high risk for PTLD (1B).
42. Seronegative patients before transplantation should be screened with EBV viral loads annually afterward to determine their susceptibility to a primary infection. Screen recipients at increased risk for EBV disease (donor-positive/recipient-negative) and PTLD weekly or biweekly during the first year after transplantation (1B).
43. Patients presenting with typical symptoms such as persistent fever and lymphadenopathy should be clinically evaluated for PTLD with histopathology and EBV viral loads. Those with rising EBV viral loads should be discussed with their transplant center; management might include reduced immunosuppression and/or specific therapy (1B).

Community-acquired Respiratory Viruses

44. Immunize recipients against community-acquired viruses (influenza A, B) annually. No guidance exists for respiratory syncytial virus

prophylaxis (1B).

Pneumocystis jirovecii

45. Give at least 6 months' prophylaxis with trimethoprim/sulfamethoxazole (1B).

Adolescent Issues

Risk Behavior

46. All adolescent girls should receive advice about fertility, contraception, and safe immunosuppression during pregnancy and should avoid mycophenolate (2B).
47. All girls with menstrual problems should be reviewed by a gynecologist for advice and management (2C).
48. Transfer adolescents who become pregnant to adult care to manage their immunosuppression (2B).
49. Inquire about prospective health insurance at the age of 17 to 19 years (depending on the locale; 2B).
50. Discuss the avoidance of substance abuse and smoking, advise minimal alcohol intake, and review risky behaviors annually (2C).

Transition to Adult Care

51. The transition process is multidisciplinary and should begin around the age of 10 to 11 years according to developmental maturity (2B).
52. Prepare a standard transition protocol involving pediatric and adult providers (2B).
53. Before the transfer, achieve readiness by building the patient's understanding of the illness, self-management skills, and ability to assume responsibility over his or her care (2B).
54. Identify an adult care group to work closely with the transferring pediatrician and the patient for at least 1 year before the transfer (2C).

Definitions:

Strength of Recommendation*

Strength of Recommendation	Criteria
1. Strong	Factors influencing the strength of the recommendation include the quality of the evidence, the presumed patient-important outcomes, and the cost.
2. Weak	There is variability in the preferences and values or more uncertainty. The recommendation is made with less certainty, or the cost or resource consumption is higher.

Quality of Evidence*

Quality of Evidence	Criteria
A. High	Further research is unlikely to change confidence in the estimate of the clinical effect.
B. Moderate	Further research may change confidence in the estimate of the clinical effect.
C. Low	Further research is very likely to affect confidence in the estimate of the clinical effect.

*Classification used by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) workgroup with minor modifications.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Any condition requiring liver transplantation

Guideline Category

Management

Prevention

Screening

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Infectious Diseases

Nephrology

Pediatrics

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide expert consensus on managing children from 3 months after liver transplant

Target Population

Children and adolescents who have undergone liver transplantation

Interventions and Practices Considered

1. Optimization of nutritional status
2. Monitoring of potential growth impairment (minimization of steroid exposure, measurement of height and weight)
3. Monitoring of body mass index and obesity management

4. Monitoring for persistent hepatic osteodystrophy, risk factors for fractures, and scoliosis
5. Vitamin supplementation
6. Assessment of school functioning and absence
7. Psychiatric assessment for post-traumatic stress disorder or other mental health issues
8. Screening of neurocognitive function
9. Assessment for hearing loss
10. Physical rehabilitation
11. Speech and occupational therapy
12. Screening for nonadherence
13. Screening for surgical complications
14. Encouraging protective clothing, screening for skin lesions, and use of sunscreen
15. Minimizing infection risks (hygiene, food, water, animals/pets, travel)
16. Travel precautions
17. Vaccination of transplant recipient and household contacts
18. Screening for and treatment of acute rejection (AR) and chronic rejection (CR)
    - Serial measurement of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), and immunosuppressant blood levels
    - Histological assessment of liver biopsy sample
    - Use of immunosuppressive therapy (e.g., tacrolimus, mTOR inhibitors, mycophenolate)
19. Screening and treatment of complications: renal function, diabetes mellitus, cardiovascular disease
20. Withdrawal of immunosuppression
21. Management of disease-specific issues and recurrent disease
22. Diagnosis and management of infections (e.g., cytomegalovirus [CMV], Epstein-Barr virus [EBV] and posttransplant lymphoproliferative disorder [PLTD], *Pneumocystis jirovecii*)
23. Special management of adolescent issues, including sexuality and sexually transmitted diseases, menstrual abnormalities, contraception, pregnancy, and nonadherence
24. Transition to adult care and self-management

Major Outcomes Considered

- Long term morbidity and mortality
- Quality of life
- Adverse effects of treatments
- Prevention and management of early postoperative complications

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

These recommendations are based on a formal review and analysis of recently published world literature on the topic (PubMed/MEDLINE search from 1996 through 2011), limited to the English language, human studies, and children 0-18 years old.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence*

Quality of Evidence	Criteria
A. High	Further research is unlikely to change confidence in the estimate of the clinical effect.
B. Moderate	Further research may change confidence in the estimate of the clinical effect.
C. Low	Further research is very likely to affect confidence in the estimate of the clinical effect.

*Classification used by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) workgroup with minor modifications.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

These recommendations are based on the following: (1) a formal review and analysis of recently published world literature on the topic; (2) *A Manual for Assessing Health Practices and Designing Practice Guidelines from the American College of Physicians*; (3) guideline policies, including the American Association for the Study of Liver Diseases policy on the development and use of practice guidelines and the American Gastroenterological Association policy statement on the use of medical practice guidelines; and (4) the experience of the authors in managing children undergoing liver transplantation (LT).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation*

Strength of Recommendation	Criteria

Strength of Recommendation	Criteria
1. Strong	Factors influencing the strength of the recommendation include the quality of the evidence, the presumed patient-important outcomes, and the cost.
2. Weak	There is variability in the preferences and values or more uncertainty. The recommendation is made with less certainty, or the cost or resource consumption is higher.

*Classification used by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) workgroup with minor modifications.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

This practice guideline was produced in collaboration with the Practice Guidelines Committee of the American Association for the Study of Liver Diseases, which provided extensive peer review of the manuscript. An external review was provided by Miriam B. Vos, M.D., M.S.P.H.

This guideline has been approved by the American Association for the Study of Liver Diseases and the American Society of Transplantation, and it has been endorsed by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate and effective long-term medical management of the pediatric patient after liver transplantation

Potential Harms

- Two-thirds of late deaths can be attributed to complications of immunosuppression, infections, and malignancies. Immunosuppression medications are associated with an increased risk for diabetes, hyperlipidemia, hypertension, obesity, and metabolic syndrome. Long-term immunosuppression treatment incurs substantial complications. The minimization or withdrawal of immunosuppression should be managed cautiously to prevent allograft damage.
- Early infectious complications tend to be related to surgical manipulations, technical complications of the surgery, and catheters and other foreign bodies. Intermediate infections are more attributable to immunosuppression, which risks infections with opportunistic pathogens (cytomegalovirus [CMV] and *Pneumocystis jirovecii*) as well as potentially severe disease from community-acquired pathogens

(respiratory syncytial virus and influenza viruses). Children with uncorrected surgical complications (bile duct stenosis and obstructions) may suffer recurrent bacterial disease.
- Avascular necrosis is a complication of high-dose steroid treatments and has been reported in 7 of 196 solid organ transplant recipients (3.6%) 9.2 years after transplantation.
- Complications of liver biopsy are relatively rare, but 2% to 5% of children may have a significant complication (usually postbiopsy bleeding).
- Other adverse effects of treatments include hirsutism, obesity, and gingival hyperplasia.
- Calcineurin inhibitors (CNI), the principal immunosuppressive medications used to prevent graft rejection, contribute to de novo acute and chronic posttransplant renal dysfunction.

Contraindications

Contraindications

- If treatment is required for late hepatic artery thrombosis, thrombolysis and anticoagulation are rarely effective, and surgical reconstruction is contraindicated.
- Chronic rejection (CR), hepatic artery thrombosis (HAT) or portal vein thrombosis (PVT) may contraindicate a repair of incisional hernia.
- Live attenuated vaccines are generally contraindicated after transplantation. Varicella vaccination is not recommended in children receiving long-term immunosuppression.
- All adolescent girls should avoid mycophenolate.

Qualifying Statements

Qualifying Statements

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Kelly DA, Bucuvalas JC, Alonso EM, Karpen SJ, Allen U, Green M, Farmer D, Shemesh E, McDonald RA. Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl. 2013 Aug;19(8):798-825. [321 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Aug

Guideline Developer(s)

American Association for the Study of Liver Diseases - Nonprofit Research Organization

American Society of Transplantation - Professional Association

Source(s) of Funding

Financial support for the development of this guideline was provided by the American Association for the Study of Liver Diseases (AASLD).

AASLD does not accept corporate support for the development of practice guidelines. However, AASLD gratefully acknowledges the support of Genentech and Merck for providing independent medical education grants for mobile download applications for AASLD practice guidelines.

Guideline Committee

Practice Guidelines Committee

Composition of Group That Authored the Guideline

Primary Authors: Deirdre A. Kelly, Liver Unit, Birmingham Children's Hospital, National Health Service Trust, Birmingham, United Kingdom; John C. Bucuvalas, Integrated Solid Organ Transplant Program, Cincinnati Children's Hospital, Cincinnati, OH; Estella M. Alonso, Division of Gastroenterology, Hepatology and Nutrition, Ann and Robert H. Lurie Children's Hospital, Chicago, IL; Saul J. Karpen, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Emory Children's Center, Atlanta, GA; Upton Allen, Department of Pediatrics, Hospital for Sick Children, Toronto, Canada; Michael Green, Division of Infectious Diseases, Children's Hospital of Pittsburgh, Pittsburgh, PA; Douglas Farmer, Dumont-UCLA Transplant Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA; Eyal Shemesh, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY; Ruth A. McDonald, Division of Pediatric Nephrology, Seattle Children's Hospital, Seattle, WA

Committee Members: Jayant A. Talwalkar, M.D., M.P.H. (*Chair*); Keith D. Lindor, M.D. (governing board liaison for the American Association for the Study of Liver Diseases); Sumeet Asrani, M.D.; Hari S. Conjeevaram, M.D., M.S.; David A. Gerber, M.D.; Marlyn J. Mayo, M.D.; Raphael B. Merriman, M.D., M.R.C.P.; Gerald Y. Minuk, M.D.; Alexander Monto, M.D.; Michael K. Porayko, M.D.; Benjamin L. Shneider, M.D.; Tram T. Tran, M.D.; Helen S. Yee, Pharm.D.

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Endorser(s)

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition - Professional Association

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the American Association for the Study of Liver Diseases Web site .

Print copies: Available from the American Association for the Study of Liver Diseases, 1729 King Street, Suite 200; Alexandria, VA 22314; Phone: 703-299-9766; Web site: www.aasld.org ; e-mail: aasld@aasld.org.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This summary was completed by ECRI Institute on December 13, 2013.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion-criteria.aspx.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical

practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.